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(54) Spherical granules having core and their production.

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Description

This invention relates to spherical granules having a core excellent in hardness and disintegration, and to their production.

Recently many studies have been made on drug delivery systems; especially as the dosage form for oral administration, granules coated with various coating agents, i.e. so-called coating granules have been used increasingly frequently, and the granules as they are or capsules produced by filling the granules in capsules have been developed.

As reasons for this fact may be mentioned that granules, as compared with tablets biopharmaceutically, reduce individual variations in gastric emptying rate, absorption, etc. and little affected by food (intake).

For production of spherical granules, the method wherein after granulation by extrusion the granules are made spherical with a marumerizer is most commonly used, but the granules thus produced are mostly not perfect spheres and the granule size distribution is wide; therefore it is said that uniform coating is so difficult that pharmaceutical preparations for precisely controlled release are difficult to be obtained.

On the other hand, recently a centrifugal fluidized-bed coating-granulator (sometimes abbreviated as CF granulator hereinafter) has been developed, and a method to make the granules spherical with this granulator has been tried.

In this method the surface of a spherical seed core or core is coated, while being sprayed with water or a solution containing a binder, with a spraying powder containing a drug, and thus spherical granules of high perfect sphere content and narrow granule size distribution are obtained. [See Drug Development and Industrial Pharmacy, 11(8), 1523-1541 (1985).]

To produce pharmaceutical preparations for controlled release the surface of the resulting spherical granules is coated with wax or polymer for the purpose of control of release of the drug. The coating is performed generally by fluidized-bed coating.

In the initital phase of the process of the fluidized-bed coating, there occur frequently troubles such as breaking and scraping of the spherical granules. These troubles not only damage the drug release control function but also affect greatly the yield in production of granules: thus a method for production of spherical granules excellent in hardness and disintegration has been desired.

EP-A-0 200 902 discloses a drug carrier capable of controlling the gastrointestinal transit rate of the pharmaceutical preparation, which comprises aqueous polymer and oil.

Under these circumstances, the inventors investigated the method for production of spherical granules excellent in hardness and disintegration by using the CE granulator, and have completed this invention.

This invention relates to

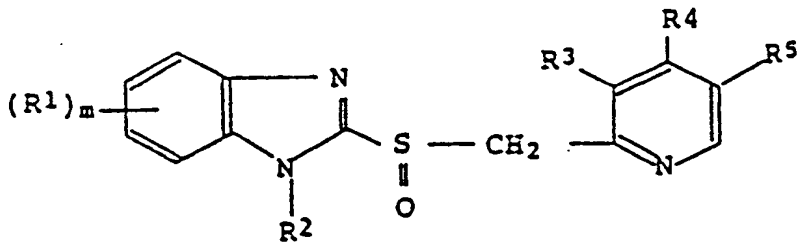
(1) spherical granules having a core coated with spraying powder containing a drug and low substituted hydroxypropylcellulose, characterized in that the drug is a benzimidazole compound having antiulcer activity

(2) a method for producing spherical granules as defined above, characterized in that seed cores are coated, while being sprayed simultaneously with an aqueous binder and with spraying powder containing a benzimidazole compound having antiulcer activity and low substituted hydroxypropylcellulose.

The content of the hydroxypropoxyl group in the low substituted hydroxypropylcellulose (sometimes abbreviated as L-HPC hereinafter) used in this invention is generally about 4 - 20 %, preferably 5.0 - 16.0 %, more preferably 10.0 - 13.0 %. The mean particle size of the L-HPC may generally be not more than 200 μm in diameter, preferably not more than 100 μm, more preferably not more than 30 μm.

The said benzimidazoles include those described in US Patent No. 4045563, US Patent No. 4255431, European Patent Publication No. 45200 US Patent No. 4472409, European Patent Publication No. 5129, British Patent Publication No. 2134523, European Patent Publication No. 174726, European Patent Publication No. 175464, and European Patent Publication No. 208452 etc.

The benzimidazoles having antiulcer activity, which are described in the above laid-open patent specifications, for instance , are represented by the formula



wherein R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifuluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R^2 is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R^4 is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4.

The compounds of the formula (I) can be produced by the methods described in the above-cited laid-open patent specifications or modifications thereof.

In the following, brief mention is made of the substituents in those compounds which have the formula (I) and are already known.

Referring to R^1 in the above formula, C_{1-7} alkyls may be mentioned as the alkyl represented by R^1; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxy; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxyalkyl and C_{1-4} alkyls as the alkyl moiety; C_{1-4} alkyls as the alkyl moiety of the carbamoylalkyl: C_{1-5} alkoxys as the alkoxy; C_{1-7} alkyls as the alkyl moiety of the hydroxyalkyl; C_{1-4}alkanoyls as the acyl; phenyl as the aryl; phenyl as the aryl moiety of the aryloxy; C_{1-6} alkyls as the alkyl moiety of the alkylthio; and C_{1-6} alkyls as the alkyl moiety of the alkylsulfinyl.

Referring to R^2, C_{1-5} alkyls may be mentioned as the alkyl represented by R^2; C_{1-4} alkanoyls as the acyl; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxy; C_{1-4} alkyls as the alkyl moiety of the alkylcarbamoyl ; C_{1-4} alkyls as each of the alkyl moieties of the dialkylcarbamoyl: C_{1-4} alkyls as the alkyl moiety of the alkylcarbonylmethyl; C_{1-4} alkoxys as the alkoxy moiety of the alkoxycarbonylmethyl; and C_{1-4} alkyls as the alkyl moiety of the alkylsulfonyl.

Referring to R^3, R^4 and R^5, C_{1-4} alkyls may be mentioned as the alkyl represented by any of them; C_{1-8} alkoxys as the alkoxy; and C_{1-4} alkoxys as each of the alkoxy moieties of the alkoxyalkoxy.

Referring to R^4, C_{1-8} alkoxys may be mentioned as the alkoxy, which may optionally be fluorinated.

More specifically, they include 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]-benzimidazole, and 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole etc.

The said seed cores include Nonpareil produced by coating sucrose (75 weight parts) with corn starch (25 weight parts) according to the per se known method, and spherical seed cores using crystalline cellulose. The drug may be used as the seed core. The particle size of the said seed cores is generally 14-80 mesh.

The said aqueous binder includes water, ethanol (concentration: preferably 50% (v/v) or less), and solutions of binders in water or in ethanol; the concentration of the said solutions is generally 0.1 - 80% (w/v), preferably 0.5 - 70% (w/v). The said binders include sucrose, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, pullulan, and gum arabic, which may be used alone or in combination.

The spraying powder containing the drug and L-HPC in this invention may be combined further with powdery additives. The said additives include excipients (e.g. lactose, corn starch, sucrose, crystalline cellulose, light anhydrous silicic acid), binders (e.g. α-starch, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, pullulan, dextrin, gum arabic), disintegrators (e.g. calcium carboxymethylcellulose, starch), stabilizers (e.g. magnesium carbonate, calcium carbonate, L-cystein), and coloring agents (e.g. talc, iron sesquioxide, tar colors).

The said spraying powder in this invention are obtained by mixing uniformly the drug, L-HPC, and the additives described above, and the particle size is generally not more than about 100 μm, preferably not more than about 50 μm.

The combination ratio of L-HPC to the spraying powder is preferably about 5 - 90% (w/w), more preferably about 10 - 60% (w/w).

The combination ratio of the drug to the spraying powder depends upon the kind and the dose of the drug, being about 2 - 70% (w/w), preferably about 5 - 50% (w/w).

In the following the method for production of spherical granules having a core of this invention is descrived in detail. The conditions under which seed cores are coated with spraying powder while being sprayed with an aqueous binder area the ratio of the aqueous binder to the spraying powder of about 1:1 - 1:2 is acequate; the production temperature need not be controlled being generally room temperature (1 - 30 °C). Spherical granules having a core of even size are obtained by sieving after drying. For example, 12 - 32 mesh round sieves are used, and the granules which pass through the 12 mesh sieve but do not pass through the 32 mesh sieve are selected.

The spherical granules having a core thus obtained may be coated according to the per se known method for the purpose of taste masking, enteric coating, gastric coating, or prolongation, and/or filled in capsules according to the per se known method.

The said coating agents include hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethyleneglycol, Tween*80, pluronic*F 68, castor oil, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit*(Röhm Pharma Co., West Germany, acrylate copolymer), carboxymethylethylcellulose, polyvinylacetaldiethylaminoacetate, waxes, and pigments such as talc, titanium oxide, ferric oxide.

The spherical granules having a core of this invention, because of their excellent hardness, can be further coated evenly (e.g. sustained release coating, gastric coating, enteric coating), and at the same time the granules are excellent in disintegration.

In the following, this invention is illustrated in detail with working examples and experimental examples.

Example 1

Nonpareils (20 - 28 mesh), 2250 g, were brought into the CF granulator (CF-360, Freund Industrial Co., Ltd., Japan), and coated, while being sprayed with 2000 ml of hydroxypropylcellulose solution (3% (w/v)) at 25 ml/min, first with the spraying powder 1 and then the spraying powder 2, both of which had been prepared by mixing the ingredients listed below, at the rate of 45 g/min at room temperature with a rotor rotating at 200 rpm, dried under reduced pressure at 40 °C for 16 hours, and sieved through round sieves, to give spherical granules having a core of 12 - 32 mesh.

[spraying powder 1]

compound A*	450 g
magnesium carbonate	450 g
sucrose	450 g
corn starch	450 g
L-HPC	450 g

(degree of substitution with hydroxypropoxyl group: 10.0 - 13.0% (w/w), mean particle size: not more than 30 µm. The particles of the same degree of substitution and particle size were used hereinafter.)

* Compound A: 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole

(* Registered Trade Mark)

[spraying powder 2]	
sucrose	420 g
corn starch	360 g
L-HPC	360 g

Example 2

The granules obtained in Example 1, 3800 g, were brought into the fluidized-bed coator (Okawara Co., Japan), subjected to enteric coating by spraying the enteric coating film solution described below at the rate of 50 ml/min under the controlled conditions of inlet air at 50 °C and material temperature at 40 °C, to give enteric coated spherical granules having core. The said granules were filled into No.2 hard capsules with a capsule filling machine (Parke-Davis Co., USA), to give capsules.

[Enteric coating film solution]	
Eudragit L30D-55	628 g
talc	192 g
polyethyleneglycol 6000	64 g
titanium oxide	64 g
Tween 80	32 g
water	4400 ml

[composition of the capsules]	
enteric coated granules	240 mg
No.2 hard capsule	65 mg
	305 mg (per capsule)

Example 3

Nonpareils (20 - 28 mesh), 1650 g, were brought into the CF granulator (CF-360, Freund Co.), and coated, while being sprayed with 1050 ml of hydroxypropylcellulose solution (2% (w/v)) at 30 ml/min, first with the spraying powder 1 and then the spraying powder 2, both of which had been prepared by mixing the ingredients listed below, at the rate of 60 g/min at room temperature with a rotor rotating at 250 rpm, dried under reduced pressure at 40 °C for 16 hours, and sieved through round sieves, to give spherical granules having a core of 14 - 32 mesh.

[spraying powder 1]	
compound A*	450 g
magnesium carbonate	336 g
sucrose	297 g
corn starch	300 g
L-HPC	354 g

* Compound A:
2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]-benzimidazole

[spraying powder 2]	
sucrose	300 g
corn starch	246 g
L-HPC	246 g

Example 4

The granules obtained in Example 3, 3800 g, were brought into the fluidized-bed coator (Okawara Co., Japan), subjected to enteric coating by spraying the enteric coating film solution described below at the rate of 50 ml/min under the controlled conditions of inlet air at 65°C and material temperature at 40°C, to give enteric coated spherical granules having core. To the said granules were added talc and light anhydrous silicic acid, then filled into No. 1 hard capsules with a capsule filling machine (Parke-Davis Co., USA) to give capsules.

[Enteric coating film solution]	
Eudragit L30D-55	2018 g (solid: 605 g)
talc	182 g
polyethyleneglycol 6000	60 g
titanium oxide	60 g
Tween 80	27 g
water	4230 ml

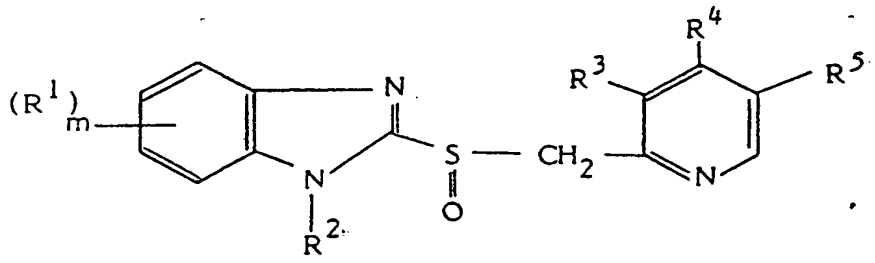
[composition of the capsules]

enteric coated granules	348.8 mg
compound A	30.0 mg
magnesium carbonate	22.4 mg
Nonpareils	110.0 mg
sucrose	39.8 mg
corn starch	36.4 mg
L-HPC	40.0 mg
hydroxypropylcellulose	1.4 mg
Eudragit L 30D-55	44.6 mg
talc	13.4 mg
polyethyleneglycol 6000	4.4 mg
titanium oxide	4.4 mg
Tween 80	2.0 mg
talc	0.6 mg
light anhydrous silicic acid	0.6 mg
No. 1 hard capsule	79.0 mg
	429.0 mg (per capsule)

Claims

1. Spherical granules having a core coated with spraying powder containing a drug and low substituted hydroxypropylcellulose, characterised in that the drug is a benzimidazole compound having antiulcer activity.

2. Spherical granules according to claim 1, wherein the benzimidazole compound is represented by the formula



wherein R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R^2 is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R^4 is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4.

3. Spherical granules according to claim 1, wherein the low substituted hydroxypropylcellulose has 4 to 20 % of the content of the hydroxypropoxyl group and is not more than 200 µm in diameter in mean particle size.

4. Spherical granules according to claim 1, wherein the spraying powder contains magnesium carbonate and/or calcium carbonate.

5. Spherical granules according to claim 1, wherein the spherical granules are further coated with spraying powder containing low substituted hydroxypropylcellulose.

6. Spherical granules according to claim 5, wherein the spherical granules are further coated with an enteric coating agent.

7. Spherical granules according to claim 6, wherein the enteric coating agent is acrylate copolymer or hydroxypropylmethylcellulose phthalate

8. A method for producing spherical granules according to claim 1, characterised in that seed cores are coated, while being sprayed simultaneously with an aqueous binder and with spraying powder containing a benzimidazole compound having antiulcer activity and low substituted hydroxypropylcellulose.

9. The method according to claim 8, wherein the seed cores are Nonpareils produced by coating 75 weight parts of sucrose with 25 weight parts of corn starch.

10. The method according to claim 8, wherein the spraying powder contains 5 to 90 % (w/w) of low substituted hydroxypropylcellulose.

11. The method according to claim 8, wherein the spraying powder contains 2 to 70 % (w/w) of the benzimidazole compound.

12. The method according to claim 8, wherein the ratio of the aqueous binder to the spraying powders is

1:1 to 1:2.

13. The method according to claim 8, wherein the spraying powder contains magnesium carbonate and/or calcium carbonate.

14. The method according to claim 8, wherein the spherical granules are further coated with spraying powder containing low substituted hydroxypropylcellulose.

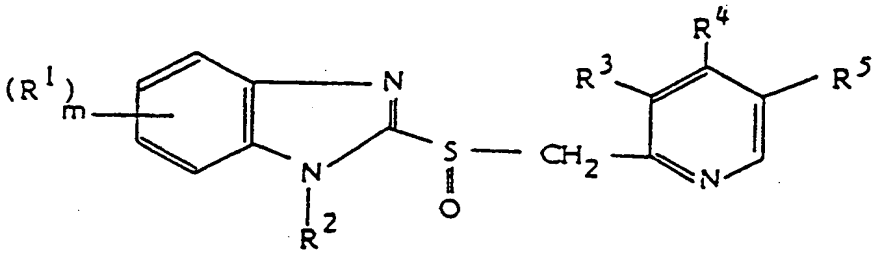
15. The method according to claim 14, wherein the spherical granules are further coated with an enteric coating agent.

16. The method according to claim 15, wherein the enteric coating agent is acrylate copolymer or hydroxypropylmethylcellulose phtalate.

Patentansprüche

1. Kugelförmige Körnchen bzw. Granulat mit einem Kern, der mit Sprühpulver beschichtet ist, enthaltend ein Arzneimittel und niedrig bzw. gering substituierte Hydroxypropylzellulose, dadurch gekennzeichnet, daß das Arzneimittel eine Benzimidazolverbindung mit Antiulkuswirksamkeit ist.

2. Kugelförmige Körnchen nach Anspruch 1, worin die Benzimidazolverbindung die Formel



hat, worin R^1 Wasserstoff, Alkyl, Halogen, Cyano, Carboxy, Carboalkoxy, Carboalkoxyalkyl, Carbamoyl, Carbamoylalkyl, Hydroxy, Alkoxy, Hydroxyalkyl, Trifluormethyl, Acyl, Carbamoyloxy, Nitro, Acyloxy, Aryl, Aryloxy, Alkylthio oder Alkylsulfinyl ist, R^2 Wasserstoff, Alkyl, Acyl, Carboalkoxy, Carbamoyl, Alkylcarbamoyl, Dialkylcarbamoyl, Alkylcarbonylmethyl, Alkoxycarbonylmethyl oder Alkylsulfonyl ist, R^3 und R^5 gleich oder voneinander verschieden sind und jedes davon Wasserstoff, Alkyl, Alkoxy oder Alkoxyalkoxy ist, R^4 Wasserstoff, Alkyl, Alkoxy, das wahlweise fluoriert sein kann, oder Alkoxyalkoxy ist, und m eine ganze Zahl von 0 bis 4 ist.

3. Kugelförmige Körnchen nach Anspruch 1, worin die niedrig bzw. gering substituierte Hydroxypropylzellulose 4 bis 20% des Gehalts der Hydroxypropoxylgruppe aufweist und die mittlere Teilchengröße nicht mehr als 200 µm im Durchmesser ausmacht.

4. Kugelförmige Körnchen nach Anspruch 1, worin das Sprühpulver Magnesiumkarbonat und/oder Kalziumkarbonat enthält.

5. Kugelförmige Körnchen nach Anspruch 1, worin die kugelförmigen Körnchen weiter mit Sprühpulver beschichtet sind, das niedrig bzw. gering substituierte Hydroxypropylzellulose enthält.

6. Kugelförmige Körnchen nach Anspruch 5, worin die kugelförmigen Körnchen weiterhin mit einem darmlöslichen Beschichtungsagens beschichtet sind.

7. Kugelförmige Körnchen nach Anspruch 6, worin das darmlösliche Beschichtungsagens Acrylatcopolymer oder Hydroxypropylmethylzellulosephthalat ist.

8. Verfahren zur Herstellung kugelförmigen Granulats bzw. Körnchen nach Anspruch 1, dadurch gekenn-

zeichnet, daß die Kornkörperchen beschichtet werden, während sie gleichzeitig mit einem wässerigen Bindemittel und mit Sprühpulver besprüht werden, das eine Benzimidazolverbindung mit Antiulkuswirksamkeit und niedrig bzw. gering substituierte Hydroxypropylzellulose enthält.

9. Verfahren nach Anspruch 8, worin die Kornkörperchen Nonpareils sind, die durch Beschichten von 75 Gew.-Teilen Saccharose mit 25 Gew.-Teilen Maisstärke erzeugt werden.

10. Verfahren nach Anspruch 8, worin das Sprühpulver 5 bis 90 Gew.-% niedrig bzw. gering substituierte Hydroxypropylzellulose enthält.

11. Verfahren nach Anspruch 8, worin das Sprühpulver 2 bis 70 Gew.-% der Benzimidazolverbindung enthält.

12. Verfahren nach Anspruch 8, worin das Verhältnis zwischen wässerigem Bindemittel und Sprühpulver 1:1 bis 1:2 ist.

13. Verfahren nach Anspruch 8, worin das Sprühpulver Magnesiumkarbonat und/oder Kalziumkarbonat enthält.

14. Verfahren nach Anspruch 8, worin die kugelförmigen Körnchen weiterhin mit Sprühpulver beschichtet werden, das niedrig bzw. gering substituierte Hydroxypropylzellulose enthält.

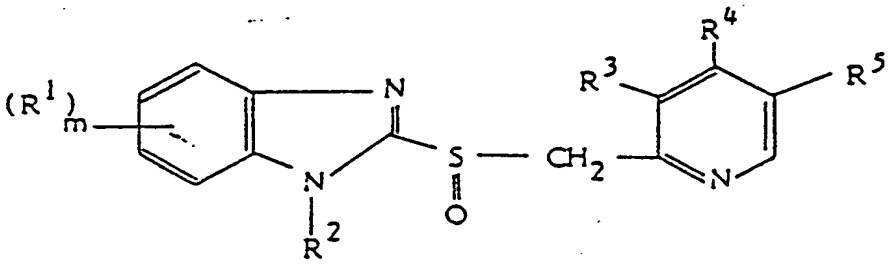
15. Verfahren nach Anspruch 14, worin die kugelförmigen Körnchen weiterhin mit einem darmlöslichen Beschichtungsagens beschichtet sind.

16. Verfahren nach Anspruch 15, worin das darmlösliche Beschichtungsagens Acrylatcopolymer oder Hydroxypropylmethylzellulosephthalat ist.

Revendications

1. Granules sphériques ayant un noyeau revêtu d'une poudre pour pulvérisation contenant un médicament et une hydroxypropylcellulose à bas degré de substitution, caractérisés en ce que le médicament est un composé benzimidazole doué d'effet antiulcéreux.

2. Granules sphériques selon la revendication 1, dans lesquels le composé benzimidazole est représenté par la formule



dans laquelle R^1 est l'hydrogène, un groupe alcoyle, halogéno, cyano, carboxylique, alcoxycarbonyle, alcoxycarbonylalcoyle, carbamoyle, carbamoylalcoyle, hydroxy, alcoxy, hydroxyalcoyle, trifluorométhyle, acyle, carbamoyloxy, nitro, acyloxy, aryle, aryloxy, alcoylthio ou alcoylsulfinyle, R^2 est l'hydrogène, un groupe alcoyle, acyle, alcoxycarbonyle, carbamoyle, alcoylcarbamoyle, dialcoylcarbamoyle, alcoylcarbonylméthyle, alcoxycarbonylméthyle ou alcoylsulfonyle, R^3 et R^5 sont identiques ou différents et chacun est l'hydrogène ou un groupe alcoyle, alcoxy ou alcoxyalcoxy, R^4 est l'hydrogène, un groupe alcoyle, alcoxy qui peut être éventuellement fluoré, ou alcoxyalcoxy et m est un nombre entier de 0 à 4.

3. Granules sphériques selon la revendication 1, dans lesquels l'hydroxypropylcellulose à bas degré de

substitution a une teneur en groupe hydroxypropoxy de 4 à 20%, et le diamètre particulaire moyen n'est pas supérieur à 200 µm.

4. Granules sphériques selon la revendication 1, dans lesquels la poudre pour pulvérisation contient du carbonate de magnésium et/ou du carbonate de calcium.

5. Granules sphériques selon la revendication 1, dans lesquels les granules sphériques sont revêtus en outre d'une poudre pour pulvérisation qui contient une hydroxypropylcellulose à bas degré de substitution.

6. Granules sphériques selon la revendication 5, dans lesquels les granules sphériques sont revêtus en outre d'un agent de revêtement entérique.

7. Granules sphériques selon la revendication 6, dans lesquels l'agent de revêtement entérique est un copolymère d'acrylate ou un phtalate d'hydroxypropylméthylcellulose.

8. Procédé de préparation de granules sphériques selon la revendication 1, caractérisé en ce que les noyaux mis en jeu sont revêtus pendant qu'on y pulvérise simultanément un liant aqueux et une poudre pour pulvérisation contenant un composé benzimidazole doué d'effet antiulcéreux et une hydroxypropylcellulose à bas degré de substitution

9. Procédé selon la revendication 8, dans lequel les noyaux mis en jeu sont des pastilles de sucre produites en revêtant 75 parties en poids de saccharose de 25 parties en poids d'amidon de maïs.

10. Procédé selon la revendication 8, dans lequel la poudre pour pulvérisation contient de 5 à 90% (poids/poids) d'hydroxypropylcellulose à bas degré de substitution.

11. Procédé selon la revendication 8, dans lequel la poudre pour pulvérisation contient de 2 à 70% (poids/poids) du composé benzimidazole.

12. Procédé selon la revendication 8, dans lequel la proportion du liant aqueux aux poudres pour pulvérisation est de 1:1 à 1:2.

13. Procédé selon la revendication 8, dans lequel la poudre pour pulvérisation contient du carbonate de magnésium et/ou du carbonate de calcium.

14. Procédé selon la revendication 8, dans lequel les granules sphériques sont revêtus en outre d'une poudre pour pulvérisation contenant une hydroxypropylcellulose à bas degré de substitution.

15. Procédé selon la revendication 14, dans lequel les granules sphériques sont revêtus en outre d'un agent de revêtement entérique.

16. Procédé selon la revendication 15, dans lequel l'agent de revêtement entérique est un copolymère d'acrylate ou un phtalate d'hydroxypropylméthylcellulose.